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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,659	12/13/2005	Andrew Austen Mortlock	101117-1P US	2270

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EXAMINER	
TRUONG, TAMTHOM NGO	

ART UNIT	PAPER NUMBER
1624	

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11/25/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,659	MORTLOCK ET AL.	
	Examiner	Art Unit	
	TAMTHOM N. TRUONG	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14 and 18-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,14 and 18* is/are rejected.

7)☒ Claim(s) *10-13 and 19-22* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

NON-FINAL ACTION

Applicant's amendment of 6-26-09 has been fully considered. The deletion of "prodrug" and "hyperproliferative disease" have overcome the previous rejections of 112/1st and 2nd paragraphs. Thus, said rejections are now withdrawn for claims 1-22. Claim 23 still recites the term "prodrug", and thus, said rejections are maintained only for this claim.

Claims 15-17 are cancelled.

Claims 1-14 and 18-23 are pending.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 8, 9 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

a. Claim 8 lacks antecedent basis because it depends on claim 7, but recites "C_{2-6}alkenyl" and "C_{2-6}alkynyl" which are not in the definition of R^7 and R^8. Furthermore, the terms "C_{2-6}alkenyl" and "C_{2-6}alkynyl" are not within the scope of "alkyl".

b. Claim 9 is not clear if it is an independent or dependent claim because it refers to claim 1 for the definitions of X, X^1, X^2, X^3, R^4 and R^5. However, the scope of other variables such as $R^{7'}$-$R^{13'}$, $R^{15'}$, $R^{16'}$ have different scope than the corresponding variables

(i.e., R^7-R^{13}, R^{15}, R^{16}) in claim 1. In particular, variables $R^{7'}$-$R^{13'}$, $R^{15'}$, $R^{16'}$ have substituents containing a "phosphonooxy" group while their corresponding variables do not have such a group.

c. Claim 23 recites the term "prodrug" which is a broad limitation followed by narrow limitation which is ester. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. **Scope of Enablement** (for prodrug): Claim 23 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making "*prodrug*" of the claimed compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The following factors have been considered in the determination of an enabling disclosure:

(1) The breadth of the claims;

(2) The amount of direction or guidance presented;

(3) The state of the prior art;

(4) The relative skill of those in the art;

(5) The predictability or unpredictability of the art;

(6) The quantity of experimentation necessary;

[See ***Ex parte Forman***, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also ***In re Wands***, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

The breadth of the claims: Claim 23 recites "prodrug" of compounds represented by formula I. The term "prodrug" covers just about any ester, amide, phosphate, sulfate having an

infinite combination of functional groups, rings, substituents, etc., and could drastically alter the structure of the parent compound. Thus, the scope of "prodrug" in claim 23 is unduly broad.

The amount of direction or guidance presented: Although the specification briefly defines what a "prodrug" is, it does not provide working examples to guide the skilled chemist to select a particular ester, amide, phosphate or sulfate for a particular site on the parent compound in order to obtain a "prodrug". Thus, the specification fails to provide sufficient enablement for making a "prodrug" of the claimed compounds.

The state of the prior art: Although it is not unusual to expect a "prodrug" of a compound, the process for selecting a particular ester, amide, phosphate, sulfate, hydrate or solvate is not standard for all drugs. For the claimed compound, there is no reference teaching any possible prodrug for these particular compounds. Thus, the state of the prior art does not support the broad scope of "prodrug" in claim 23.

The relative skill of those in the art: Even with the advanced training, the skilled clinician would have to engage in extensive research to select a particular "prodrug" for each compound from the large Markush group of formula I. Not only one has to determine an IC_{50} value, but also *in-vivo* activity to establish an LD_{50}, therapeutic index and active metabolites for each "prodrug". Given a large Markush group of the claimed formula, such a task would require a tremendous amount of effort, time and resource.

The predictability or unpredictability of the art & The quantity of experimentation necessary: The process of making a prodrug requires three criteria: (1) the "prodrug" must be biologically inactive; (2) the "prodrug" must be metabolized into the active drug at a

physiologically meaningful concentration; (3) the active drug must still have the intended biological activity. Many prodrugs produce additional active metabolites (*in- vivo*) that do not have the same chemical structure of the intended drug. Thus, the process of making a prodrug is highly unpredictable due to many unknown *in-vivo* factors as well as uncertain numbers of active metabolites with potential adverse effects.

Thus, with such a limited teaching from the specification and the art, the skilled chemist would have to engage in undue experimentation to make the hundreds of thousands of compounds covered by "prodrug"of compounds represented by formula I in claim 23.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

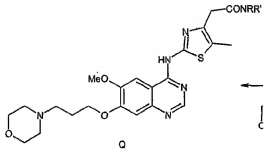
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

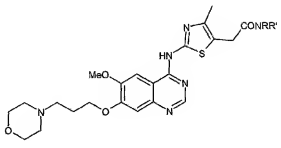
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. Claims 1-8, 14 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Mortlock et. al.** (WO 02/00649 A1 cited on IDS). On page 90, Mortlock discloses a formula Q with the following structure:



Q

TABLE 19



N°	NRR'
561	aniline
562	3-chloro-4-fluoroaniline
563	2-aminopyridine
564	3,4-difluoroaniline

Said formula is analogous to a compound of formula (I) with the following substituents:

i. R^1 is hydrogen;

ii. R^2 is $-X^2R^{12}$; X^2 is oxygen; R^{12} is an alkyl group;

iii. R^3 is $-X^3R^{13}$; X^3 is oxygen; R^{13} is a heterocyclylC_{1-4}alkyl group;

iv. R^4 is hydrogen;

v. $-NHR^5$, wherein R^5 is an aryl or heteroaryl group substituted with a halogen or amino group.

The disclosed compound differs from the claimed compound by not having a 1,2,3-triazolyl group bonded to –HN- group at the 4-position. However, the generic formula I on page 3 of WO'649 defines variable R^5 (of $-XR^5$) to include triazole of no particular arrangement of the ring nitrogen atoms, see the following paragraph on page 7:

> Examples of 5-membered aromatic rings R^5 include rings containing one or more heteroatoms selected from sulphur, oxygen and nitrogen. Such rings include pyrrole, pyrazole, pyrazolone, imidazole, oxazole, furan, tetrazole, triazole, thiazole, thiophene, or thiadiazole, any of which may be optionally substituted. In particular, R^5 includes at least one nitrogen or sulphur heteroatoms. Preferred rings for R^5 include pyrrole, pyrazole, imidazole, triazole, thiazole, thiophene, or thiadiazole.

Like the claimed compounds, Mortlock's compounds are also used to treat breast and colon tumours (e.g., see page 2, lines 15-16). Thus, one skilled in the art would have been motivated to modify Mortlock's compounds by having a 1,2,3-triazole at the position of R^5 (of -

XR^5 in WO'649) because such a modification would have still maintained the same pharmacological activity to treat tumours.

In view of the recent ruling in KSR, the court determines obviousness based on what a skilled artisan would have known at the time of the invention, and on what such a person would have reasonably expected to have been able to do in view of that knowledge (***KSR, 82 USPQ 2d, 1385***). In other words, the decision in KSR forecloses the argument that a **specific** teaching, suggestion, or motivation is required to support a finding of obviousness.

Thus, at the time of the invention, it would have been obvious to select and make compounds claimed herein in view of the teaching above.

Claim Objections

4. Claim 10-13 and 19-22 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The process recited in claim 19 differs from the process taught in WO'649 by not reacting a starting material having an amidine group with a heteroaryl group having a carboxylate group.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TAMTHOM N. TRUONG whose telephone number is (571)272-0676. The examiner can normally be reached on M, T and Th (9:00-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Tamthom N. Truong/
Examiner, Art Unit 1624

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624

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11-19-09